**Oesophageal Cancer**

**Model Structure**

**Natural History**

The model updates information on each individual with regard to oesophageal cancer status every 3 months. The model structure is described in Figure 1 and parameters give in Table 1.

*Incidence of Low-Grade Oesophageal Dysplasia*

Table 2 describes the parameters and their values. Jointly, the chosen parameter values produce the model outputs shown in Table 3.

Informed by incidence rates of oesophageal cancer from Malawi cancer registry (Chasimpha et al, 2017), incidence of low-grade oesophageal dysplasia is assumed to occur in people from age 20 years onwards and to depend on age, sex, and tobacco intake. The rate per 3 months in men aged exactly 20 without excess alcohol or tobacco use is assumed to be 0.00001. Informed by Chasimpha et al 2017, Banda et al 2001, Moses et al 2017, the rate ratio for females is taken as 1.3-fold. The rate ratio per year older after age 20 is assumed to be 1.1, consistent with the 100-fold increase in rate between age 20 and 70 observed in Chasimphia et al, 2017. Informed by Mlombe et al 2017, the rate ratio for tobacco smoking is 2.0. We include a parameter for an effect of excess alcohol intake but use a rate ratio of 1.0 as Mlombe et al 2017 suggests this is not an independent risk factor.

*Progression between dysplasia / cancer stages*

Informed by Kastelein et al we assume a probability per 3 months of high-grade oesophageal dysplasia, amongst people with low grade dysplasia of 0.03. Likewise, informed by Kastelein et al 2014 and Verbeek et al 2012 (albeit this is mainly adenocarcinoma when Malawi has preponderance of squamous cell carcinoma, but prognosis is not greatly different), the probability per 3 months of stage 1 oesophageal cancer amongst people with high grade dysplasia is 0.01.

Progression through stages of oesophageal cancer are informed by survival according to stage at diagnosis. The 5-year survival in United States (with treatment availability): 45% stage 1/2, 24% stage 3, 5% stage 4)[[1]](#footnote-1). The 5-year survival without surgery < 5% Kauppila et al 2018 (Sweden). The probability per 3 months of stage 2 oesophageal cancer amongst people with stage 1 oesophageal cancer is taken as 0.05, as is the probability of progression from stage 2 to 3, and from stage 3 to 4.

*Experience of dysphagia*

We assume a probability per 3 months of symptoms of dysplasia being experienced in a person with stage 1 oesophageal cancer of 0.1, with a rate ratio for dysplasia of 0.1 for low- or high-grade dysplasia, reflecting the lower chance of symptoms at this stage. Likewise, the rate of experience of dysplasia is assumed to increase with stage, 3-fold for stage 2, 4-fold for stage 3 and 5-fold for stage 4. Presence of dysplasia leads to healthcare seeking.

*Rate of death from oesophageal cancer*

Probability per 3 months of death from oesophageal cancer amongst people with stage 4 oesophageal cancer is assumed to be 0.4 per 3 months.

**Treatment for Oesophageal Dysplasia / cancer**

At all stages of dysplasia/cancer except stage 4 cancer there can be medical treatment aimed at cure amongst people who are diagnosed (which we refer to as curative treatment, recognising that it is often not successful in achieving a cure). Depending on stage this might include surgery, radiotherapy, chemotherapy [Feedback required on this point].

Persons on treatment are assumed to have a lower risk of progression to the next successive stage; but if they do progress to the next stage, there is no further effect of treatment. The rate ratio for the effect of treatment on progression for those with low-grade dysplasia, high-grade dysplasia, stage1 and stage2 is 0.1, based on indirect evidence from Kauppila et al 2018. For progression from stage 3 to stage 4 the rate ratio is taken to be 0.4, which is also based on indirect evidence from Kauppila et al 2018.

We recognise that availability if treatment is currently extremely limited in Malawi: there were reported in 2015 to be five Malawian oncologists and haematologists involved in full-time cancer care in the whole country (Masamba et al, 2015).

**Disability weights**

* For persons with any stage of cancer prior to stage 4 and have never had any treatment, a disability-weight of 0.288 is applied, corresponding to "Diagnosis and primary therapy phase of oesophageal cancer: Cancer, diagnosis and primary therapy, has pain, nausea, fatigue, weight loss and high anxiety”.
* For persons with any stage of cancer prior to stage 4 and have ever had any treatment, a disability-weight of 0.049 is applied, corresponding to "Controlled phase of oesophageal cancer, Generic uncomplicated disease: worry and daily medication, has a chronic disease that requires medication every day and causes some worry but minimal interference with daily activities”
* For persons with a cancer in stage 4 and with no palliative care, a disability-weight of 0.451 is applied, corresponding to “Metastatic phase of oesophageal cancer: Cancer, metastatic: has severe pain, extreme fatigue, weight loss and high anxiety."
* For persons with a cancer in stage 4 and with no palliative care, a disability-weight of 0.451 is applied, corresponding to “Metastatic phase of oesophageal cancer: Cancer, metastatic: has severe pain, extreme fatigue, weight loss and high anxiety."
* For persons with a cancer in stage 4 and with palliative care, a disability-weight that is applied that is equal to those with earlier stage cancers without treatment.

**Health System Interactions**

*Care Seeking & Diagnosis*

Dysphagia is assumed to trigger healthcare seeking to a Non-Emergency Generic Appointment at Facility Level 1, whereupon referral to further health system interaction is indicated. In that appointment, an investigation using an endoscope is undertaken. If that investigation confirms Oesophageal Cancer and if the stage of cancer is not stage 4 then the patient is referred to initiate treatment. If the cancer is confirmed and is in stage 4, the patient is referred to Palliative Care.

We aim for these rates to eventually be informed by data on stage of oesophageal cancer at diagnosis from the cancer registry, although in the initial report from the registry for very few cancer cases was there a cancer stage at diagnosis recorded (Msyamboza et al, 2012).

*Treatment Initiation & Monitoring*

Treatment is implemented for the patient in a separate single appointment, following diagnosis of any form of stage prior to stage 4 (low/high grade dysplasia and stages 1-3). The patient is monitored every year thereafter, and if the patients has progressed to stage 4, the patient is initiated on Palliative Care.

*Palliative Care*

Patients initiated on palliative care remain on palliative care and received a monitoring appointment each month. No benefit for the patient is in effect.

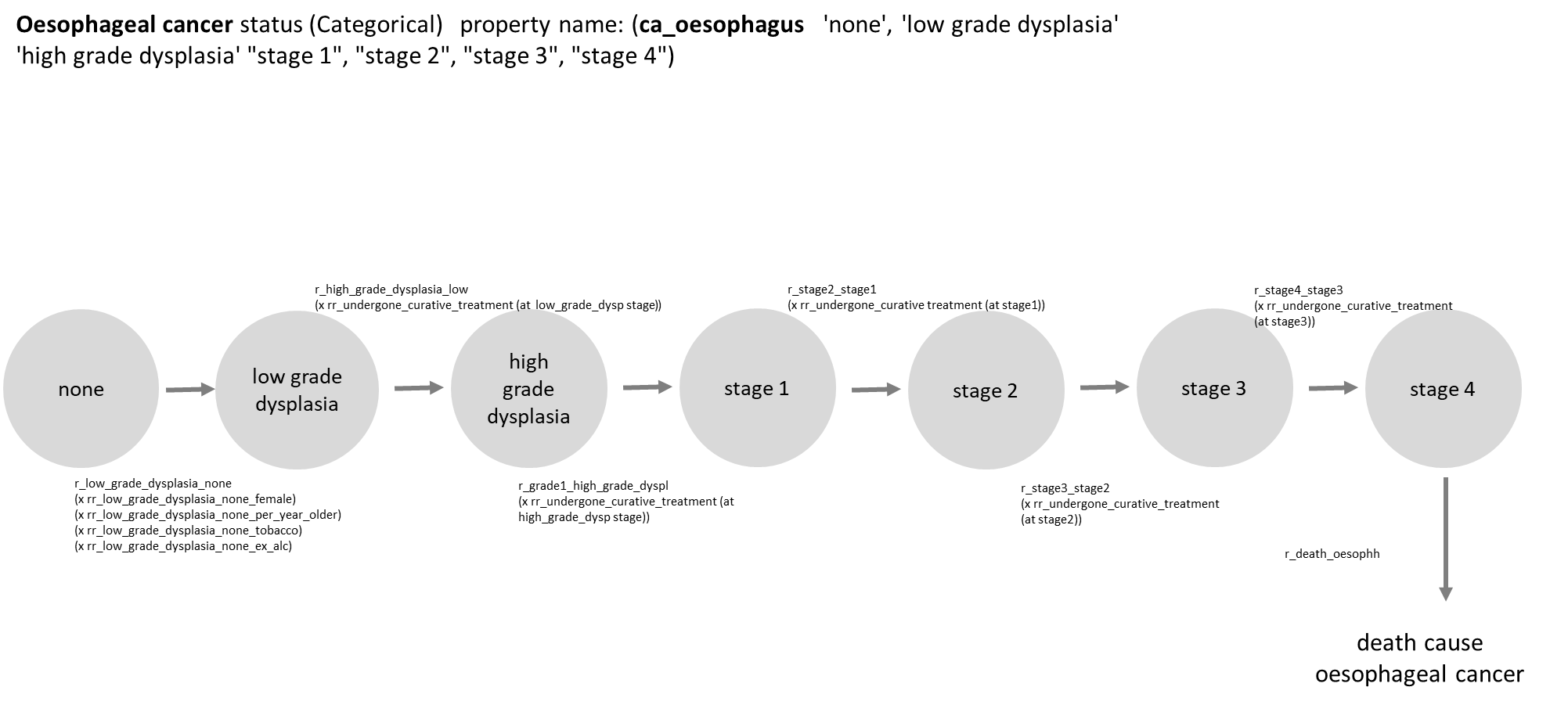
**Main Limitations**

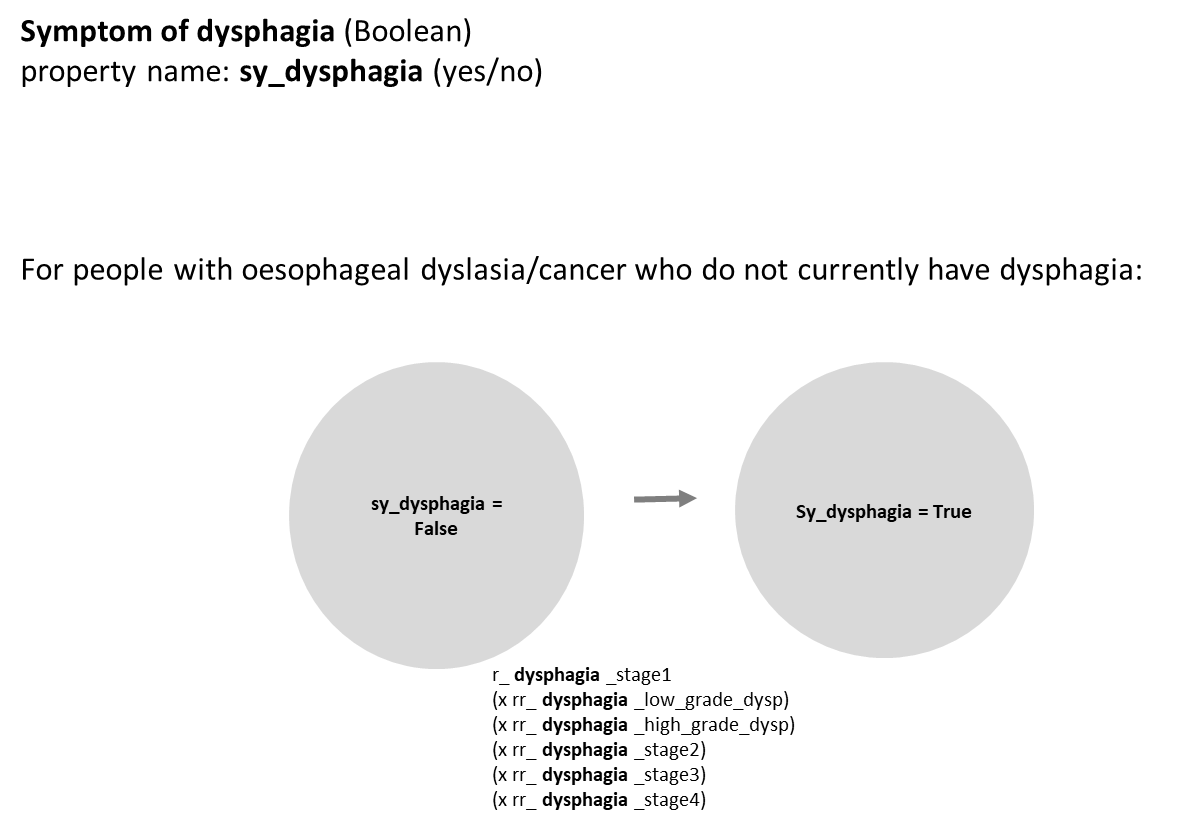
The main limitations are the relative lack of data to directly inform many of the parameter values. Underlying progression of the condition is assumed to follow a similar course as in studies in other parts of the world. For incidence of low-grade dysplasia (as the first stage in the path of progression to oesophageal cancer) and rates of diagnosis and availability it is necessary to consider data from Malawi itself given that these are likely to depend on the setting. As it becomes possible to perform more analyses in collaboration with the cancer registry, we expect to be able to further inform our parameter values.

**Calibration**

See Table 2.

**Figure 1. Diagrams illustrating model structure and parameters.**

**(a) Oesophageal Cancer Status**

**(b) Symptom of Dysphagia**

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 2. Description of parameters and proposed values** | | | |
| **Parameter** | **Proposed value** | **Description** | **Notes** |
| r\_low\_grade\_dysplasia\_none | 0.0000005 | probability per 3 months of incident low grade oesophageal dysplasia, amongst people with no oesophageal dysplasia (men, age20, no excess alcohol, no tobacco) | in conjunction with rate ratios below, informed by incidence rates of oesophageal cancer from Malawi cancer registry (Chasimpha et al, 2017) |
| rr\_low\_grade\_dysplasia\_none\_female | 1.3 | rate ratio for low grade oesophageal dysplasia for women | Chasimpha et al 2017, Banda et al 2001, Moses et al 2017 |
| rr\_low\_grade\_dysplasia\_none\_per\_year\_older | 1.1 | rate ratio for low grade oesophageal dysplasia per year older from age 20 | rate increases 100 fold between age 20 and 70 (Chasimphia et al, 2017) |
| rr\_low\_grade\_dysplasia\_none\_tobacco | 2 | rate ratio for low grade oesophageal dysplasia for tobacco smokers | Mlombe et al 2017 |
| rr\_low\_grade\_dysplasia\_none\_ex\_alc | 1 | rate ratio for low grade oesophageal dysplasia for no excess alcohol | Mlombe et al 2017 suggests not an independent risk factor |
| r\_high\_grade\_dysplasia\_low | 0.03 | probability per 3 months of high grade oesophageal dysplasia, amongst people with low grade dysplasia | Kastelein et al 2014 |
| rr\_high\_grade\_dysp\_undergone\_curative\_treatment | 0.1 | rate ratio for high grade dysplasia for people with low grade dysplasia if had curative treatment at low grade dysplasia stage | indirect evidence from Kauppila et al 2018 |
| r\_stage1\_high\_grade\_dyspl | 0.01 | probability per 3 months of stage 1 oesophageal cancer amongst people with high grade dysplasia | Kastelein et al 2014; Verbeek et al 2012 (mainly adenocarcinoma when malawi has preponderance of SCC, but prognosis is not greatly different) |
| rr\_high\_grade\_dysp\_undergone\_curative\_treatment | 0.1 | rate ratio for stage 1 oes cancer for people with high grade dysplasia if had curative treatment at high grade dysplasia stage | indirect evidence from Kauppila et al 2018 |
| r\_stage2\_stage1 | 0.05 | probability per 3 months of stage 2 oesophageal cancer amongst people with stage 1 oesophageal cancer | see \* below |
| rr\_stage1\_undergone\_curative\_treatment | 0.1 | rate ratio for stage 2 oes cancer for people with stage 1 oesophageal cancer if had curative treatment at stage 1 | some evidence from Kauppila et al 2018 |
| r\_stage3\_stage2 | 0.05 | probability per 3 months of stage 3 oesophageal cancer amongst people with stage 2 oesophageal cancer | see \* below |
| rr\_stage2\_undergone\_curative\_treatment | 0.1 | rate ratio for stage 3 oes cancer for people with stage 2 oesophageal cancer if had curative treatment at stage 2 | some evidence from Kauppila et al 2018 |
| r\_stage4\_stage3 | 0.05 | probability per 3 months of stage 4 oesophageal cancer amongst people with stage 3 oesophageal cancer | see \* below |
| rr\_stage3\_undergone\_curative\_treatment | 0.3 | rate ratio for stage 4 oes cancer for people with stage 3 oesophageal cancer if had curative treatment at stage 3 | some evidence from Kauppila et al 2018 |
| r\_death\_oesoph | 0.4 | probability per 3 months of death from oesophageal cancer amongst people with stage 4 oesophageal cancer | see \* below |
| r\_dysphagia\_stage1 | 0.01 | probability per 3 months of diagnosis in a person with stage 1 oesophageal cancer | low probability of diagnosis before symptoms appear - probability likely to increase with grade of cancer - looking for data on stage of oesophageal cancer at diagnosis from cancer registry |
| rr\_dysphagia\_low\_grade\_dysp | 0.01 | rate ratio for dysphagia if have low grade oesophageal dysplasia | as above |
| rr\_dysphagia\_high\_grade\_dysp | 0.01 | rate ratio for dysphagia if have high grade oesophageal dysplasia | as above |
| rr\_dysphagia\_stage2 | 2 | rate ratio for dysphagia if have stage2 oesophageal cancer | as above |
| rr\_dysphagia\_stage3 | 50 | rate ratio for dysphagia if have stage3 oesophageal cancer | as above |
| rr\_dysphagia\_stage4 | 100 | rate ratio for dysphagia if have stage4 oesophageal cancer | as above |

\* progression rates informed by survival according to stage at diagnosis (5 year survival in United States (with treatment availability): 45% stage 1/2, 24% stage 3, 5% stage 4) https://www.cancer.org/cancer/esophagus-cancer/detection-diagnosis-staginsurvival-rates.html; 5 year survival without surgery < 5% Kauppila et al 2018 (Sweden).

\*\* treatment access: Six private and public medical oncology units have been established, spanning all three regions of the country. These can administer cytotoxic chemotherapy under the supervision of either an oncologist or a haematologist and other experienced doctors. This has enabled management of most chemotherapy-sensitive tumours. Radiotherapy not available (Masamba 2015). Queen Elizabeth Central Hospital in Blantyre has a single procedure room and is a World Gastroenterology Organisation International Endoscopy Training Centre forming the centre of a hub-and-spoke endoscopy training programme for the three other central hospitals in the country. It performs around 1200 upper gastrointestinal endoscopies per annum, of which 300 are therapeutic—mainly dilatation or stenting of squamous cell carcinoma and banding of oesophageal varices. Thirty-nine per cent (620 patients) underwent bougie dilatation of their tumour for symptom relief, 11% (179 patients) had placement of a self-expanding metal stent (only sporadically available in our hospital), and one patient had alcohol injection of the tumour for debulking. Two perforations were identified after bougie dilatation and were managed conservatively. One per cent (17 patients) underwent an Ivor Lewis oesophagostomy with end-to-end anastomosis and 1% (22 patients) had palliative gastrostomy tubes inserted. Seventeen per cent (274 patients) received chemotherapy. Though palliative stenting has good efficacy in our setting (<4% complication rate and a median survival of 210 days),7 the cost is unfortunately prohibitive for the health service and for patients, and as such, bougie dilation is often undertaken. There is a paucity of evidence of long-term outcomes for this procedure though it seems effective in other settings22 and carries

a risk of malignant perforation. (Chetwood et al. 2018).

**Table 2. Model outputs and observed data from Malawi**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Model Output** | **Observed Data** | **Notes** |
| 5 YEAR SURVIVAL FOLLOWING TREATMENT |  |  |  |
| Number of incident diagnoses of oesophageal dysplasia per year (low / high grade) | < 100 | --- | No data identified |
| Number of incident diagnoses of oesophageal cancer per year (total; stage 1, 2, 3, 4) | 1285 (300, 300, 465, 220) | 620 | Derived from Msyamboza et al 2012 \* |
| Incidence rate of diagnosed oesophageal cancer (all stages combined) / 100,000 population aged ge 20 | 15 | 25.3 | Derived from Chasimpha et al 2017. \*\* (considered to be some under-ascertainment) |
| Current total number of people who have diagnosed oesophageal cancer (total; stage 1, 2, 3, 4) (including people who have been given attempted curative treatment for stage 1 oesophageal cancer at some point in the past and have not progressed to a higher grade) | 5,250 (1150, 1600, 2300, 200) | --- | No data identified |
| Number of people given attempted curative treatment for low grade oesophageal dysplasia per year | 0 | --- | No data identified – assumed currently low. |
| Number of people given attempted curative treatment for oesophageal dysplasia per year (total; low, high grade) | < 100 | --- | No data identified – assumed currently low. |
| Number of people given attempted curative treatment for oesophageal cancer per year (total; stage 1, 2, 3, 4) | < 100 | --- | No data identified – assumed currently low. |
| Number of deaths from oesophageal cancer | 560 | --- | No data identified but 620 identified cases of oesophageal cancer per year, most reported to be identified at late stages. New death registration system should provide data in future. |

\* 18,946 new cases of cancer in 44-month period 2007 – 2010; 12.0% oesophageal, implying 620 new cases of oesophageal cancer diagnosed per year in Malawi. Registry covers 96% of relevant clinics in Malawi.

\*\* 368 cases in Blantyre 2008-2010 from population 248,728 men and 236,355 women age greater than or equal to 20 = crude rate 25.3 / 100,000 population aged > 20.

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